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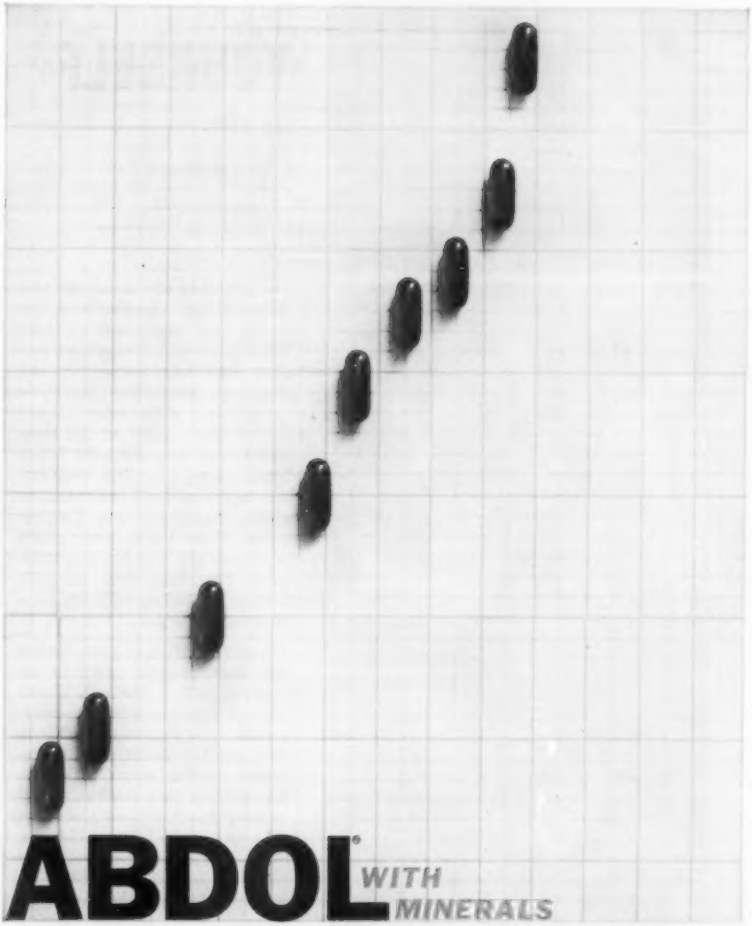

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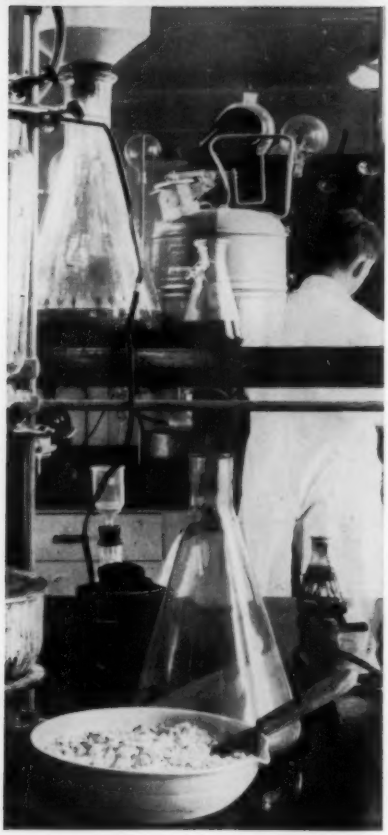

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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E D I T O R I A L

Project HOPE

MOST Americans, and surely all engaged in any one of the health professions, have heard of Project HOPE, but some may not understand its full significance and the opportunity which each of us has in supporting this most unusual project both to help others and improve our country's relations abroad.

Project HOPE is the principal effort of the People-to-People Health Foundation, Inc. which has fully equipped and staffed the S. S. Hope I, a floating medical center and teaching hospital. This hospital ship of mercy and medical teaching is to travel the world over to those underdeveloped areas lacking adequate medical facilities. Presently, the ship is in Indonesia where it will remain for some time both treating native populations and, even more importantly, training local physicians and others in the health professions to better serve their people.

This project is completely financed by the American people and without government subsidization which makes it all the more significant. The cost for the first year is estimated to be three and a half million dollars and over two million have already been contributed. Pharmacists are being asked to make their contributions to this worthy enterprise, and a special Project Hope Committee under the chairmanship of Thomas A. Foster in Washington, D. C. has been organized in order to solicit pharmacists for their financial assistance. We wish to give this effort our strong endorsement and we surely hope that pharmacists will rally to this worthy cause both as a part of their professional obligation and, even more importantly, as a means of improving our country's prestige and esteem abroad.

One cannot help but compare the billions of dollars which this country has spent overseas in equipping our so-called "allies" to be more efficient in destroying human life and the return which we have received from this investment with the relatively inexpensive Project HOPE and the return which is its potential. While we do not pose as having more knowledge and judgment than our leaders in government concerning what is best for the future of the United States, we

have been somewhat dismayed over some of the consequences of our expenditures for arms and munitions abroad. It has also been quite unfortunate that many of these instruments of destruction eventually have found their way into the hands of our enemies, thence to be used against some of our friends as well as ourselves.

While we doubtlessly have contributed to the strength of some of our allies and presumably helped fortify our position against world Communism, the psychology of this effort is somewhat perilous, as anyone understanding human nature could have anticipated. Armies and armaments are in so many places throughout the world the agencies of human repression and even oppression. Often they provide the means of keeping civilian populations—even those who are good citizens but having a different political philosophy—under control. In so using them, they are certain to stir up hatred not only toward those who have them but for the country who supplies them and makes their purchase possible.

It would seem to us that much of our foreign policy in this regard has been unfortunate and not as effective as other efforts to send teachers and technicians to assist the underdeveloped countries in improving their social and economic status rather than in maintaining their *status quo*.

Project HOPE is something which we predict will make such a dramatic impression for good in faraway places overseas that it may well cause our own government to reconsider the direction and emphasis in which our assistance overseas is to be given. No-one—not even our enemies—can criticize our acts of mercy and kindness freely given, without political implications, and with no obligation or thought of return. If America's position overseas is ever to regain the place which it once held in the eyes of the world, it will be such things as this which accomplish it. We call upon all pharmacists to send to the Project Hope Committee their contributions for this truly American effort.

L. F. Tice

Send contributions to:

Thomas A. Foster, Chairman
Project Hope Committee, A. Ph. A.
Box 9808
Washington 15, D. C.

A CHRONOLOGY OF ATHEROSCLEROSIS

By Thomas H. F. Smith *

THE development of man's knowledge and understanding of the vascular anomaly now designated "atherosclerosis" has been long and tortuous. The singular factor which retarded this advancement appears to have been one of semantics. The majority of the early investigators neglected to establish conformity of expression with their contemporaries. Without uniform terminology, the attempts of one individual to interpret the work of another frequently led to misconceptions and often disagreements. A survey of the literature revealed that a surge of progress followed soon after the establishment of precise criteria and descriptions of each of the various forms of this vascular disease.

The chronology of this knowledge can be considered as being divided into three periods. In terms of time, these periods are designated as "The Period Prior to 1833," "The Period From 1833 to 1908," and "The Period From 1908 to the Present Time." Each of these eras is distinguished by a specific event, the occurrence of which signalled a profound advance in the understanding of this vascular disease. The choice of certain incidents as milestones is no indication that the other discoveries and observations of the period were of less importance.

Certain events from each of these periods are presented here to provide a perspective of the development of the knowledge of atherosclerosis.

The Period Prior to 1833

Aristotle (384 B. C.) and his contemporaries (1) commented on their gross anatomical studies. Prominent among their observations were descriptions of "bone-in-the-heart," but they offered no suggestions as to the cause or significance of this condition.

The medical literature from the time of Aristotle until the 1500's was speckled with an abundance of postulations and theories, either

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in support or in criticism of some previously published observation or concept.

Among the more significant reports are those of Benivieni (2), who described an undesignated arterial lesion, the description of which closely resembled the characteristics of the disorder now designated arteriosclerosis, and Fallopio (3), in 1575, who reported on a woman whose arteries on one side had "turned to bone." During this period the emphasis was centered on the hardening of the vessel walls, which was designated as "ossification of the arteries."

Bellini (4) theorized that the petrifactions of the arteries resulted from an inflammation of the wall and the subsequent formation of a "crust." Brunner (5) described an aorta which contained bone-like plaques throughout, especially conspicuous in the abdominal areas. He also observed that the internal arterial wall was ruptured, and in several places lacerated like rotten fruit. This is one of the first reports on the softening of the vessel in this vascular pathology.

The 18th Century was notable for the appearance of many important works in vascular anatomy, physiology, and pathology. This era marked the turning point for the beginning of modern pathological research. The "anatomical-idea" was the byword in pathology. All attention was focused on the part of the body which was the site of the disease. As knowledge, techniques, and instrumentation improved, smaller and smaller units of the human structure were examined. The organization of the arterial wall into three distinct histological layers became evident and this information intensified the effort to localize more accurately the site of the vascular lesion.

Speculation on the nature and etiology of these vascular alterations was carried to excess. An esteem for the great men of antiquity frequently clouded the intellect of scientists and because of this they formulated fallacies and misconceptions. Despite the fact that numerous important contributions were made in this time, much erroneous thinking occurred during this period and retarded the progress of knowledge of these vascular diseases for many years.

Crell (6), in 1740, proposed a concept which proved influencing. He rationalized that the "incrustations," universally spoken of as "ossifications," were not in fact bony at all but suggested that the lesions were derived from "pus," the fluids of which had evaporated while the thicker portion hardened. Crell also observed that this induration was not confined to senile persons but could occur at any

age. He localized the site of these scales as occurring between the intima and the media of the artery.

Following in this direction, von Haller (7), in 1755, likewise placed more importance on the soft element of the lesion, which he termed "atheromatous." It should be noted that the word "atheroma" had been used in the medical literature from the time of the early Greeks to describe any closed sac or cyst of noninflammatory origin, and filled with gruel-like substance or pus. The activities of Crell and von Haller transferred the attention of other investigators from the hardening to the softening process in this complex vascular degeneration.

A more complete and comprehensive description of the lesions was given by Morgagni (8) than by any of the previous authors. He made repeated inferences to the relationship of the atheromatous plaques and the condition now known as dissecting aneurysm. Morgagni is credited with associating "pain in the chest" with "ossification of the arteries of the heart." It is thought today that over 85 per cent of all cases of coronary artery insufficiency are due to an atherosclerotic involvement and the manifest symptom of this condition, now termed angina pectoris, is a "pain in the chest." In his descriptions and writings, Morgagni directed attention to the special involvement of the aorta and the coronary arteries, the vessels of the extremities, of the brain, and of the spleen. He proved that the vascular plaques were not osseous tissue by demonstrating that pus and other pathological materials produced the same odor as the plaques when incinerated. He also struck a blow at the senescence theory, which indicted senility as the causative factor, by citing the case of a woman of ninety in whom "sclerotic" lesions were minimal.

In 1800, Bichat (9) took opposition to Morgagni's findings and again attributed vascular degeneration to the aging process. Hodgson (10), on the other hand, published an extensive treatise on diseases of the blood vessels in which he concluded that these vascular lesions were definitely pathological and not a natural phenomenon of advancing life. Hodgson compared the atheromatous lesions to ulcers of the small bowel, and mentioned the sloughing of the plaque and the disappearance of the curdy matter into the blood stream. He chemically analyzed the material of the plaque and concluded from the constituents that it could not be of an osseous nature. He also localized the site of the lesion in the intima of the vessel.

The end of this period was heralded by the coining of the new word "Arteriosclerosis" by Lobstein (11), in 1833. This term was accepted to designate in a generic way many of the vascular anomalies previously reported. At this same time, Lobstein confirmed Hodgson's analysis of the plaque as definitely not osseous, although he found a slightly higher organic content than his contemporary had previously reported.

The Period From 1833 to 1908

With the problem of nomenclature temporarily resolved and the establishment of a uniform terminology for vascular diseases, interest shifted to the etiology of these conditions.

Cruveilhier (12) focused his investigations on intravascular clotting and, although his thinking was advanced, his conclusions were unfortunately erroneous. He reasoned that the circulating blood transported the putaceous matter of the atheromatous lesion to the site and then produced the inflammation of the vascular wall. The putaceous material was supposedly then replaced by the local clotting of the blood, functioning as a repair mechanism. Cruveilhier's astute remarks on his observations portended numerous aspects of the situation which were not developed or appreciated until many years later.

Continuing with the analysis of blood components, Carswell (13) illustrated a case of gangrene of the toes which he attributed to the ossification of the arterial wall and the deposition of fibrin in the lumen of the vessels.

In 1841, Rokitansky (14) published extensive discussions on the ". . . excessive deposition in the inner membrane of the vessels." He proposed that these depositions were derived primarily from fibrin and other endogenous substances of the blood mass, rather than some type of purulent exudate. The importance of fibrin formation in vascular degeneration was apparently overlooked by the investigators of this period and the further examination of this aspect of the problem was neglected for many years.

In America, Vogel (15) ignored fibrin and identified cholesterol as the major constituent of atherosclerotic plaques.

Virchow (16), in the meantime, concentrated on the "sick cell" as the *ense morbi* or essence of disease. His works formed conspicuous contributions to the knowledge and progress of vascular

pathology during the latter part of the 18th Century. In his analysis of the succession of events which occurred in the course of this disease, Virchow deduced that the alterations were not due entirely to passive degeneration. Rather, he asserted, there was an increase in tissue ground substance followed by an active proliferation of the connective tissue of the intima. He assumed that both of these activities were the results of a fatty metamorphosis of the connective tissue and a softening of the intermediate ground substance.

Credit for distinguishing between this proliferative degeneration and ordinary fatty degeneration of the intima, without a preliminary overgrowth of connective tissue, is given to Rindfleish (17), a pupil of Virchow.

Gull and Sutton (18) conducted careful microscopic researches on the blood vessels in health and disease in an attempt to discern the nature of the various vascular lesions. They contributed the suggestion that a "hyalin fibroid" rearrangement was conceivably involved in the destruction of the vessels.

A quarter of a century later, Jores (19), employing greatly improved histological techniques, ascribed a prominent role to the elastic tissue in vascular regeneration processes. He investigated the proliferative capacities of this tissue and evaluated the retrogressive modifications which appeared when it was subjected to stress. In addition, he demonstrated its influence upon the organization of thrombi in the intact artery.

The first years of the new century were marked by the findings of Mönckeberg (20) on medial calcinosis. He stressed the fact that this condition was a unique entity, separate and distinct from the intimal forms of arteriosclerosis. His proposal was accepted and is today designated as Mönckeberg's sclerosis.

At the Twenty-first Congress for Internal Medicine, held at Leipzig in 1904, Marchand (21) recommended the adoption of the term "Atherosclerosis", which he considered to describe the complete course of this pathology of the vessels. The components of the word are derived from the Greek, "athero" meaning mushy, and "sclero" meaning hardening. This term was an attempt to compromise both those who ascribed prime significance to fatty degeneration and those to whom calcification and hardening was of foremost importance. Reluctance to the acceptance of this new word as a generic term arose for several reasons. The more evident of these objections was

the lack of specificity as to the layer of the vessel involved. The findings of Virchow (16) and other investigators previously mentioned were overlooked.

To clarify this muddled state of affairs, Klotz (22) proposed another approach to the terminology problem. "Let us preserve the broader meaning (of the term) and regard all sclerosis or hardenings of the arteries as included under this general term (arteriosclerosis), recognizing, if need be, distinct varieties." This motion met with general acceptance and formed the basis for the classification of the degenerative arteriopathies which is in use today. Under the generic heading *Arteriosclerosis,* were included the subdivisions *atheromatosis, atherosclerosis, Mönckeberg's sclerosis,* and *hyperplastic arteriosclerosis.* These entities included all the progressive changes of the arterial walls caused by hyperplasia and secondary depositions which result in abnormalities of the vascular tissues. Klotz' contribution can be considered an important event of this period.

Throughout medical history, the diseases of man and persistent attempts to produce comparable conditions in animals have been constant companions. Investigators have long entertained the hope that through the experimental production of a disease state an insight into its etiology would be gained. The failures of experimental efforts prior to 1908 are now attributed largely to a lack of a clear-cut idea of exactly what type lesion to produce. It should be remembered that, prior to 1906, there was no agreement as to the distinguishing characteristics of the individual entities of this extensive group of vascular pathological conditions.

Mechanical injury from ligating, pinching, wounding, and cauterizing the arteries of animals produced inflammatory changes but no lesions similar to those seen in man (23-27). Several authors (28, 29) reported arterial changes which resulted from irritating or severing certain nerves but these results were not confirmed (21, 24, 30).

In 1903, Josue (31) produced lesions of a sclerotic nature in rabbits by repeated injections of epinephrine. These lesions occurred in the media and were characterized by the calcification of this layer (Mönckeberg's sclerosis). Only small, insignificant quantities of lipid substance were detected in these arteries.

A vast array of toxic substances and bacterial cultures and derivatives were administered with uniformly negative results. Either

arterial changes failed to appear or they were entirely dissimilar and unrelated to those seen in human conditions.

The Period 1908 to the Present Time

Selection of the years from 1908 to the present time as a single period was made to unify the events of importance in the development of experimental methods for the production of vascular diseases, particularly atherosclerosis.

In 1908, Ignatowsky (32) published the results of his experimental feeding of animal protein to rabbits. He was concerned primarily with the effect of the protein and other unnatural foods on the metabolism and renal function of herbivores. He reported that pronounced aortic changes occurred. These changes consisted of intimal thickening and the appearance of giant cells resembling those seen in human atherosclerotic conditions.

Saltykow (33) employed a staphylococcal-alcohol combination which he claimed caused fatty masses in the intimal thickenings. These results were never attained by those who attempted to repeat his work (34, 35).

Other experiments by Starokadomsky and Ssobolew (35), who combined a diet of eggs with experimentally elevated blood pressure, led to the conclusion that intimal hypertrophy was caused by a mechanical factor and lipoid degeneration was due to a toxic effect of protein.

Stuckey (36, 37) and Wesselkin (38) demonstrated that the decisive factor for the development of experimental atherosclerosis was not the protein but the fatty substance. However, they did not think it was lecithin or the neutral fats.

This finding preceded the work of Anitschkow and Chalatow (39), who produced atherosclerosis in the rabbit by feeding cholesterol dissolved in vegetable oil. This study confirmed Lemoine's earlier suggestion about the involvement of cholesterol (40), which he had based on chemical studies of the contents of human atherosclerotic arteries, obtained at autopsies.

Following the work of Anitschkow and Chalatow (39), numerous investigators reappraised the protocols of their earlier experiments. Saltykow, who had initially attributed the production of atherosclerosis to the administration of staphylococci and alcohol,

corrected his error and made known (41, 42) that, in this experiment, the animals had been fed large quantities of milk, thus unwittingly incorporating cholesterol. Kon and Yamada (43) re-evaluated other investigations on feeding animal protein to herbivores and concluded that the organ (liver) used as protein in the diet was high in cholesterol content.

During this period of uncertainty and the exploration of experimental methods, many negative results were reported by investigators who were unable to produce atherosclerotic lesions with a dietary cholesterol regimen. This was considered insignificant and of small consequence then, in view of the many positive findings which appeared concurrently.

In 1933, Anitschkow (44) presented a survey of the history of experimental atherosclerosis. In this commentary there appeared an unobtrusive remark, apparently included as a casual explanation of the unsuccessful efforts of some previous authors. The portent and magnitude of this remark which was overlooked at this time warrant its quotation here. He said:

> "It should be mentioned that the various investigators prepared their cholesterin solutions with different vegetable oils. It is not impossible that the particular kind of oil used for this purpose might have some influence on the absorption of cholesterin from the intestine, and also on the rapidity and intensity of the atherosclerotic changes in the arteries."

It is unfortunate that so many years passed before this phenomenon was rediscovered, and the activity of vegetable "oils" was evaluated clinically in the treatment of atherosclerosis.

In this same commentary, Anitschkow clearly and extensively described the macroscopic and microscopic appearance of the lipid plaques of the aorta and other arteries of the rabbit which resulted from cholesterol feeding. He observed that the regressive stages of this process could be represented in the same manner that the progressive changes were discerned. This regression occurred after discontinuance of the cholesterol diet. He revealed that as the lipoidal substances of the lesion were slowly reabsorbed the plaque was gradually transformed into partially hyalinized fibrous connective tissue, often containing large quantities of calcium. These events might well be considered the "sclerotic" phase of the over-all atherosclerotic

process in the same fashion that the lipid accumulation is designated "atherogenic."

Several poignent notations on the etiological factors of experimental atherosclerosis were also enumerated by Anitschkow (44). The first was that "the process always begins with the accumulation of lipoid substances in the intercellular substance of the innermost layers of the arterial walls." In elaborating on this, he directed attention to the fact that the lipid was not a degeneration product of the arterial wall, since the histological composition of this structure remained normal even after the appearance of the lipid accumulations. Nor was it derived from mucoid material as he showed by chemical analysis. Secondly, these lipid aggregations only became evident after feeding the animals a high cholesterol content diet for prolonged periods. The parenteral introduction of cholesterol did not produce any atherosclerotic change, even when injected as a colloidal suspension intravenously (45-47). The investigations on intravenous cholesterol administration followed the realization that extremely high levels of circulating serum cholesterol occurred after the alimentary absorption of appreciable quantities of this lipid substance.

Anitschkow also revitalized some of his previous conclusions recalling that "atherosclerosis is not essentially of degenerative nature, but rather of an infiltrative character" (48, 49). The examination of the lipoidal materials in polarized light (44) showed them to be composed of ". . . a mixture of various lipoids, containing particularly large quantities of cholesterin esters." Finally and perhaps most significant, by controlled experiments with a colloidal stain (trypan blue), he showed (50, 51) that "there is also under normal conditions a constant stream of liquid passing through the walls of the arteries in the direction from the lumen to the adventitia."

With the criteria of Anitschkow to serve as a guide, numerous investigators ventured to produce atherosclerosis experimentally in various animal species. The most successful production of experimental atherosclerosis resulted from cholesterol feeding, either alone or in combination with some other modification. A detailed discussion of methods for the production of experimental atherosclerosis is beyond the scope of this presentation. Katz and Stamler (52) reviewed the literature on experimental atherosclerosis up to 1953.

Through the years, many objections were levelled against the choice of the rabbit as a suitable animal in which to produce and study

atherosclerosis. The critics reasoned that the rabbit was too dissimilar to man to yield information adaptable to comparison (53-55). Despite the fact that he first proposed the rabbit for use in the study of experimental atherosclerosis, Anitschkow (44) noted the disparities between atherosclerosis occurring in this species and in man, at least a decade prior to his modern censors.

The chick was mentioned in the literature in 1914 (56) as a possible choice for experimental atherosclerosis studies. Proponents of the chick advanced cogent reasons for choosing it as an experimental subject. Dauber (57) commented that "of all animals, birds have arteriosclerosis most closely resembling human arteriosclerosis." He also noted that the chick, like man, was omnivorous, and considered that this added to the significance of the results obtained with this animal.

Use of the rat as an experimental subject for the study of atherosclerosis was largely a development of the years after 1950 (58).

After experimental atherosclerosis was firmly established as a laboratory tool in the early 1930's, the task developed of improving upon the methods to produce conditions more nearly comparable to those seen in the human. The experimental approach advanced the study of the etiology and pathogenesis of the disease and made feasible the investigation of various prophylactic and therapeutic substances. In both cases, the use of animal subjects permitted the study of large, unform, and easily controlled samples in which multiple variables could be conveniently evaluated.

Atherosclerosis had emerged by the end of the 1930's from the position of a medical curiosity. It was no longer considered a casual observation at autopsies, but was now regarded as a major cause of death.

The first attempt to correlate the available information on this subject, on an international basis, was the symposium sponsored by the Josiah Macy, Jr. Foundation. The exchange of concepts and information which took place at this meeting were edited by Cowdry (59) and published in 1933 titled "Arteriosclerosis." Following this meeting, there was an accelerated advancement of the knowledge of vascular pathologies.

By 1954, it became evident that a survey of the developments which took place since 1933 was essential. A symposium was held under the auspices of the National Academy of Sciences on the general

aspects of the atherosclerosis problem recognized at that time. The results of this symposium were later published (60).

During the years between 1933 and 1954, a tendency developed on the part of researchers to direct their investigations toward specific areas of these vascular conditions, rather than attempt to study broad general aspects. It is interesting to reflect briefly upon these various areas and examine their historic origin and some of the advances which have been recently reported.

As previously mentioned, Cruvhielier (12) in 1835 and Rokitansky (14) in 1841 both expressed the possibilities of blood components being involved in the various vascular pathologies which they had observed. Both suggested the idea of a "fibrin nidus" origin of degenerative lesions of the vessel wall. Virchow (16) and Rindfleish (17) reported similar findings to those of their predecessors. Anitschkow (44) likewise mentioned ". . . a secondary reactive hyperplasia of the fibrous elements of the vascular wall in response to lipid infiltration which resulted in the formation of connective tissue plaques." This facet of the problem received little further attention until 1946 when Duguid (61) elaborated more extensively on the subject. His work was subsequently repeated and verified by a number of investigators during the early 1950 period.

The role of connective tissue in atherogenesis continued to occupy an important position in the growing accumulation of knowledge A survey of the information on connective tissue and its relationships to the atherosclerotic process was prepared by Tunbridge (62) in 1957. Wolstenholme and O'Connor (63) reviewed the role of mucopolysaccharides in relation to vascular abnormalities in 1958.

In this same year, Page organized a meeting of scientists, not specifically engaged in atherosclerosis investigations, but prominent in the fields of blood and connective tissue research. The results of this symposium, published in 1959 (64), served both to elaborate further the knowledge of the role of blood and connective tissue in relation to atherosclerosis. It also stimulated additional interest in atherosclerosis in individuals versed in collateral disciplines.

Returning again to the comments of Anitschkow (44), it is seen that he sagaciously cautioned against describing cholesterol or hypercholesterolemia as the "cause" of atherosclerosis. He advised that it be considered as only one of the many etiological factors involved. Explaining this concept further, he emphasized the dependence of the

atherosclerotic process upon both the "intensity" and "duration" of the cholesterol disturbance and included in addition a suggestion that "other lipoids" might be inculpated in addition to cholesterol. Kritchevsky (65) and Cook (66) published comprehensive treatises on cholesterol in 1958. Katz, Stamler, and Pick pursued the question of the role of cholesterol in this disease for many years. They summarized their early reviews with a volume on "Nutrition and Atherosclerosis" (67) in 1958.

Despite the intensive examination which has been made, the precise part which lipids play in atherosclerosis (68, 69) has not been determined conclusively at the time of this writing.

Another avenue of approach to the development of atherosclerosis was the hormonal actuation of atherogenesis. This likewise had been previously discerned by Anitschkow (44). He referred in his remarks to ". . . metabolic disturbances induced by interfering with internal secretions." He postulated that atherosclerosis resulted not from a singular alteration or cause, but rather from a combination of modifications of physiological mechanisms in the body. In view of this, he designated it a "metabolic disturbance disease." This theory is still tenable today.

Dury (70) in 1959 edited a publication on the subject of hormonal-atherosclerotic relationships. This subject was also discussed in detail in a book prepared by Pincus (71) in this same year. It is interesting to note that the first of these contributions emphasized hypertension-atherosclerosis relationships and the latter devoted a chapter exclusively to emotional factors as predisposing or aggravating causes of this vascular pathology.

Here once more appeared the outcropping of an observation of Anitschkow (44), for he had previously pointed to "influences of a nervous nature," as an etiological component of this disease process.

Summarizing the development of knowledge of atherosclerosis from the beginning to the present time shows that certain concepts are agreed upon as basic ingredients of this process. Without attempting to debate the validity and merits of the various and diversified tenets on atherogenesis, the major premise might be stated as follows: *Atherosclerosis* is a distinct disease entity. It is identified with related but intrinsically different vascular pathologies under the broad-spectrum term, *arteriosclerosis*. With respect to incidence and mortality, it is the most important of these conditions. Considered as

a disease, *atherosclerosis* is not inevitable nor irreversible. It can be spoken of as preventable and, up to a point, curable. The etiology of this abnormality is not singular, but attributable to a complex and variable interinvolvement of many separate physiological factors.

Time is a vital component in the development of this syndrome, not necessarily in terms of the normal process of chronological aging or senility, but with respect to the duration of the modifications and derangements of normal body metabolism.

Cholesterol is regarded as a major factor, critically, but not exclusively involved. Alterations of the normal metabolic mechanisms which affect cholesterol, lipids, and lipoproteins characterize the presence of this disease.

Disturbances of hormonal balances often predispose, accelerate, or aggravate the progress of this degenerative process. Elevations of blood pressure similarly affect atherogenesis.

Hereditary predisposing influences, with regard to both lipid disorders and the effects manifest by "reactions to stress," also appear to be involved in atherogenesis.

Summary

The span from 1908 to 1960 was marked by many profound advances and contributions to the knowledge of atherosclerosis. Although significant progress has been made toward an understanding of the etiology of this disease since Anitschkow, the findings of the last decade have elaborated and supported, rather than contradicted, his postulations. Unfortunately, despite exhaustive and penetrating explorations, many perplexing aspects of this disease process remain to be explained before a solution can be realized.

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A NOTE ON THE SOLUBILITY OF SALICYLIC ACID IN ISOPROPANOL-WATER SOLUTIONS AT 25° C.*

By Nathan A. Hall **

IN the course of formulation studies with salicylic acid, it became necessary to discover its solubility in various isopropanol-water mixtures. An experiment was devised for attaining saturation equilibrium modified from the method of Bowey (1).

Experimental

Isopropanol—Commercial isopropylalcohol (British Drug Houses) was treated with calcium oxide and fractionally distilled under anhydrous conditions. Mixtures of purified isopropanol and distilled water were prepared by weight.

Salicylic Acid—Salicylic Acid B. P. was recrystallized twice from 70% ethanol and dried in a vacuum oven at 60° C.

Method—A triplicate series of test tubes containing the percentages of isopropanol shown in Table I was prepared, and to each tube an excess of powdered salicylic acid was added. The tubes were closed with previously washed, rubber stoppers, shaken vigorously for three minutes and set aside for three weeks at room temperature (approximately 29° C.). During the waiting period, the samples were shaken at least once daily with care to assure the dispersion of the compacted mass of salicylic acid at the bottom of the tube. The samples were next placed in a thermostatically controlled water bath at 25° ± 0.1° C. for another two weeks during which time daily shaking was continued. Evidence of attainment of saturation equilib-

* This investigation was conducted in the laboratories of the Department of Pharmaceutics, University of Malaya, Singapore while the author was a visiting professor under the Fulbright program (1959-60). The technical assistance of Mr. Tang Pak Seong is gratefully acknowledged.

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rium was shown when the assay of the sample containing 50% isopropanol was the same on two subsequent days.

The solutions were assayed for salicylic acid after removal of a sample with a pipet protected against withdrawal of undissolved crystals by glass wool. All solutions were titrated with standard (0.5 to 0.01 N) sodium hydroxide solution. In addition, those containing distilled water alone and 10% isopropanol were analyzed colorimetrically. The absorbance of the color formed upon the addition of ferric chloride solution was measured at 525 millimicrons in a Unicam Quartz Spectrophotometer. The results, representing the average of triplicate determinations, were recorded in Table I.

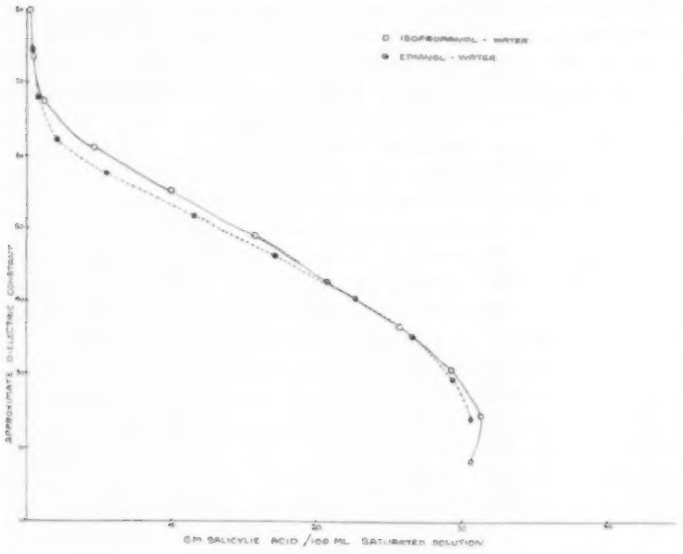

FIGURE 1

A plot of the approximate dielectric constant of ethanol-water and isopropanol-water mixtures against the solubility of salicylic acid at 25° C.

Discussion

In the light of the publication by Moore (2) which advocates the use of the approximate dielectric constant for predicting solubility in solvent mixtures for formulation, it is interesting to compare the data obtained in this study with that of Seidell (3) who determined the solubility of salicylic acid in ethanol-water mixtures. In Figure 1, the solubility of salicylic acid is plotted against the approximate dielectric constant (ADC) of the solvent as calculated by the method of Moore (2). The predicted solubility, based upon the ethanol-water system of Seidell, shows fairly good correlation with the experimental data. Such agreement would be expected, since similar solvation forces are probably involved. Solubility predictions by this method are often poor when large differences in solute-solvent interactions occur; however, for rapid, practical utilization where the polarity of the solvent is the primary consideration in solubility, Moore's method can be regarded as an approximate but useful tool.

TABLE I

SOLUBILITY OF SALICYLIC ACID IN AQUEOUS ISOPROPANOL SOLUTIONS AT 25° C.

Isopropanol % by weight	*Salicylic Acid Gm./100 ml.*
0	0.224
10	0.373
20	1.099
30	4.64
40	9.99
50	15.77
60	20.74
70	25.73
80	29.37
90	31.4
100	30.6

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SOME OBJECTIVES OF THE N. A. B. P.*

By Ralph M. Ware, Jr.**

THE basic objective of the National Association of Boards of Pharmacy is set forth in Article II of the Constitution:

> "The purpose of the Association is to provide for interstate reciprocity in pharmaceutic licensure, based upon a uniform minimum standard of pharmaceutic education and uniform legislation; to improve the standards of pharmaceutical education and licensure by cooperating with state, national and international agencies and associations having similar objects."

Through the years, I do not believe any fair-minded person could dispute the fact that the Association has endeavored to carry out this objective.

In an association of boards representing 52 states and territories, each of which operate under individual constitutions, individual laws and rules, and under different conditions with respects to the pattern of pharmaceutical practice, it has always been surprising to me to note how much uniformity has been achieved. At the risk of being labeled a "moss-backed reactionary," I would like to observe that at times a lack of complete uniformity sometimes turns out to be the greatest strength we have. When you become completely uniform, you may become completely regimented and the danger of complacency, which may breed mediocre performance, becomes a threat. As far as reciprocity is concerned in pharmacy, we have better machinery than most of our sister professions. Most candidates have no difficulty going from one state to another state.

I would agree that we should continue to upgrade our requirements, consistent with their practical administrative application in the interest of better pharmaceutical practice. The important thing is to have basic agreement on principles so that all pharmacists residing in a reciprocity state are not barred from licensure in another state on technical grounds alone. A resolution coming from this district relative to more uniform practical experience requirements has been referred to the Committee on Internship for study.

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* Presented before District No. 2 Conference of State Boards and Colleges of Pharmacy, October 7, 1960, Wilmington, Delaware.

** President of the National Association of Boards of Pharmacy.

I consider this matter a continuing fluid thing that will be changing from time to time because of the continuing changes in the pattern of pharmaceutical practices in the field which are dictated by the times in which we live. Certainly this will continue to be an important objective of the N. A. B. P., and I certainly propose, during my term of office, to have the appropriate N. A. B. P. Committee on Internship give thoughtful consideration to this subject.

One other Resolution dealing with the question of examinations, which also came from District 2, was considered by the N. A. B. P. at its recent convention.

I think it wise to enumerate the ten broad aims and objectives of the examination seminar held annually by the N. A. B. P. They are as follows:

1. To define the objectives and purposes of the licensing examination.
2. To identify the area in pharmaceutical education where the licensing examination properly belongs.
3. To separate the concepts of educational and fitness testing.
4. To identify and study the major areas to be covered in the licensing examination.
5. To obtain a greater degree of uniformity among the licensing examinations of the various states.
6. To improve the quality of the licensing examinations.
7. To establish a more equivalent level among licensing examinations from state to state.
8. To publish as a permanent record and guide for examiners in the major fields the proceedings and recommendations of which may be incorporated in the recommended outline of the Association.
9. To maintain a more vigilant and understanding attitude toward progress and changes in the field of education and pharmaceutical practice.
10. Finally, to encourage interest and develop programs for all problems directly related to the responsibility of pharmaceutical licensure: Internship problems, reciprocity, foreign graduates, etc.

In reference to the resolution adopted in this district last year on the subject of examinations, I am personally in favor of amending the by-laws of the N. A. B. P. to provide that member boards not be required to examine candidates in specific subjects and, in lieu thereof, be required to give an examination for licensure as a pharmacist, embracing all the subject matter. This can be accomplished by utilizing the already existing material, as it is now provided by our national office and made available to member boards if the boards want to use it. Most boards use it. There is no reason why the N. A. B. P. could not engage the services of experts to assist in compiling and formulating good examination questions in all areas of pharmacy. State boards utilizing this type of examination procedure would not bar their licensees from reciprocating to other states, if the by-laws were amended as outlined. The convention recommended that the resolution covering this broad subject be referred to the Committee on Examinations for study and a report on the feasibility of its implementation.

In the stated objectives of the N. A. B. P., I think it is reasonably clear that the purpose of the N. A. B. P. is to continually strive to improve the standards of pharmaceutical practice in the interests of the public.

This brings me to the one great objective I believe the N. A. B. P. should initiate in the interests of American pharmacy. Stated quite simply, it is my judgment that the N. A. B. P. should initiate a study that would eventually lead to the formulation of a New Model Pharmacy Act. By way of review, may I call your attention to a resolution which was referred by the American College of Apothecaries to the A. Ph. A. at the recent convention? It is as follows:

> "Whereas, there is a distinct and serious need for greater uniformity in the Pharmacy Acts within the several states
>
> "Be It Resolved, that the American College of Apothecaries urge the American Pharmaceutical Association to make every effort to study the existing state laws and with the guidance of various individuals and groups construct a Uniform State Pharmacy Act which could be utilized by each of the states in a legislative effort to modernize their existing laws consistent with the needs and demands of our modern day practice of pharmacy and of the public."

The A. Ph. A. referred this resolution to the N. A. B. P. and it will be taken up by the Executive Committee to deal with at the 1961 convention. I am in accord with this resolution. Such a study should be carried out under the auspices of the American Pharmaceutical Association, and various organizations in pharmacy should be called upon to contribute their time, talent, and money. The N. A. B. P. has sufficient resources to contribute to such an objective, and it is a proper function of the organization to do so, in my opinion.

It is pertinent to note that in 1932 the proposed "Uniform State Pharmacy Act" was recommended by an A. Ph. A. Committee on Modernization of Pharmacy Laws. In 1946, the proposed Barbiturate Law was recommended by the National Drug Trade Conference.

The type of study I have in mind would not be directly related to a review of the manufacturing and distributing aspects of pharmacy. The proper place for this rests with the National Drug Trade Conference, I believe. Just what am I talking about? It is this: We accept as fact that the practice of pharmacy is a professional function, regardless of where it is practiced, and yet we still have no great over-all objective in motion that would secure this end.

Throughout the years, I submit our emphasis has been on securing orderly distribution of drug products as commodities of commerce, and we have tried desperately to reconcile this function of pharmacy with our professional function. In doing this, we have become purveyors of merchandise. This is our *national image*. Maybe this is the way it should be, but my information leads me to conclude that most pharmacists don't like it. Forces at work in our economic life have contributed to this *image*, but has the profession completely fulfilled its responsibility to offset this image? I think not—and, if not, why not?

The fact is that a five-year course of education is incompatible with what the recipient of that education must face when he enters into the practice of pharmacy as a practitioner; and I support the five-year program 100%. It is not reasonable to pass it off with the statement that in a few years everything will change because the men coming into the field will be better educated. This is unrealistic and history does not bear it out.

What should we do? Well, we should do many things, all of which will require much research. You have got to look where you have been, and where you are, in order to determine where you wish to go—and it cannot be done with snap judgment.

1. We should examine once again the proposition of whether it is really in the public interest for non-pharmacists and corporations to "own," if you please, a pharmacy—and I am aware of the right to ownership of private property under the terms of our Constitution.
2. We should establish what a pharmacy is or should be. Should any outlet be permitted to open a "pharmacy"?
3. We should examine carefully how much effect forces outside of pharmacy, both political and economic, are having in dictating the policies of professional practice. How much professional freedom has been lost because of these forces?

I don't have the answer to any one of these and I suspect you do not either. This would be a big undertaking. It would require expert legal talent that would be costly, and many dedicated men who would have to work over a period of time. The time is here to set in motion a study that would lead to establishing a broad national purpose for the professional practice of pharmacy. This purpose should then be reduced to specific objectives that could then be implemented in the form of recommended law. I submit that we do not have such a purpose now, which is in the interests of all pharmacists and the public.

In arriving at a "purpose," the emphasis should be placed on the interests of the public. If we believe that the public is not receiving the best possible professional pharmaceutical service within the framework of statutory requirements now in effect, then we should feel secure in this undertaking, and enter into it with zeal and enthusiasm. If we believe that the public is satisfied, that the majority of pharmacists everywhere are satisfied, and that the future of our *younger pharmacists* is secure in a free enterprise profession within the framework of existing statutes, then we should forget this proposal.

Many may say it is too late, but I am not willing to admit it until it can be proven with overwhelming evidence. As a board officer, I see daily, step by step, the increased difficulty we have in regulating the practice of pharmacy as a professional function in our society. If the quality of pharmacy practice and professional practice deteriorates, then we have not fulfilled our responsibility as pharmacists to the public.

I was struck with the address of President Ronald Robertson of the A. Ph. A. when he succeeded to the presidency. All of what he said was good, but I was particularly impressed with his closing remarks: "It has been said that without vision the people perish. Without vision the profession of pharmacy will slide into crass commercialism under the umbrella of bureaucracy. Only great faith and great vision can undo the blights of recent hours."

I still do not believe that a profession can solve all of its problems in the halls of Congress or the halls of the state legislatures. Certainly we have contributed to the high standard of medical care now prevailing in this country under existing conditions and existing laws, but I take the position that we have reached a point where the professional posture of the practicing pharmacist is questioned. If we believe that a reaffirmation of this professional posture is *absolutely necessary* to preserve a high standard of medical care for all Americans in the years ahead, then we had better re-examine our legal role in the entire scheme of medical care.

I appreciate the privilege you have given me to speak to you in my capacity as President of the N. A. B. P. I am not a pessimist. I am a realist, and sincerely believe that I have accurately stated the issue that confronts the practicing pharmacist today.

THE UNIQUE PLACE OF FOLIC ACID ANTAGONISTS IN CONTROLLING MALIGNANT BLOOD DISEASES

By John R. Sampey *

FOLIC acid antagonists are the agents of choice in the management of the acute leukemias. A current review (19) shows that these antimetabolites were employed in the treatment of 3114 patients in 182 published clinical reports. Another review, however (20), indicates that folic acid antagonists find little application in the control of related diseases, such as chronic granulocytic leukemia, chronic lymphocytic leukemia, lymphosarcoma, Hodgkin's disease, and polycythemia. On the other hand, it is not unusual to find cytostatic drugs like nitrogen mustards, myleran, triethylene melamine, 6-mercaptopurine, urethan, adrenal steroids, and radioactive phosphorous being used in two or more different malignant lymphomas and reticuloses (20).

Several reviews (3, 9, 31) have judged the action of folic acid antagonists as contraindicated in the chronic leukemias, Hodgkin's disease, lymphosarcoma, and reticuloses. The present study was undertaken to determine just how limited has been the use of these antimetabolites in the treatment of malignant blood diseases, other than the acute leukemias, during the last decade.

Chronic Granulocytic Leukemia

More than a dozen investigators have conducted clinical trials of folic acid antagonists (FAA) on chronic granulocytic leukemia. In accordance with the recommendations of a panel of hematologists [*Blood 4*, 89-96 (1949)], chronic granulocytic leukemia embraces the more commonly used term, chronic myelocytic leukemia, also. In 1949, Burchenal *et al.* (6) treated nine patients with 4-aminopteroyl glutamic acid and noted that seven showed some improvement. Two years later (8), these investigators reported that one adult had a good remission on FAA and six showed partial remissions in 16 cases. Spigliati and Galardeschi published two reports in 1953 on

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the relation of citrovorum factor (CF) to FAA: in one study (25), they described brief remissions in five patients after treatment with CF but, in another investigation (26), they found no response in four patients treated with a combination of CF and aminopterin. J. C. and L. T. Wright and associates (32, 33) tested several FAA on adults with chronic granulocytic leukemia and, in one report, they described two objective remissions in six patients and, later, they reported similar changes in two other cases. Berman *et al.* (2) secured some hematological response in all five patients with aminopterin, but they noted no subjective improvement and the toxic reactions were bad. Mendonca (13) induced one brief partial remission in three patients treated with this antimetabolite, and Meyer *et al.* (14) had no response in three adults. Solari (23) also noted little response in three chronic granulocytic leukemias after aminopterin and amino-an-fol therapy. Schweisguth and Denoix (22) employed a combination of aminopterin and hormones in children to secure survivals of seven out of eight for two to six years. Heinle (11) described some clinical and hematological improvement in two adults on a folic acid deficient diet after administration of crude FAA preparations, but the effect was temporary. Reinhard *et al.* (17) employed amino-an-fol in two patients with advanced stages of granulocytic leukemia without any benefit. Sullivan *et al.* (27) secured a complete hematological remission for four weeks with a combination therapy of methotrexate given intra-arterially and CF given intramuscularly. Brahin *et al.* (3) described a two months' clinical and hematological remission after large doses of folic acid, but paresthesias of the toes developed and treatment was discontinued. Mickle *et al.* (16) recorded no improvement in one patient with chronic granulocytic leukemia following a combination of X-rays and aminopterin therapy. Isaacs and Trimmer (12) had a patient develop pernicious anemia on aminopterin therapy.

Chronic Lymphocytic Leukemia

In 1950, J. C. Wright *et al.* (32) reported clinical and hematological remissions in three patients with chronic lymphocytic leukemia who received FAA therapy and, the following year, L. T. Wright *et al.* (33) reported some improvement in three of four patients but they observed no complete remissions and noted the toxic effects of

the drugs. Berman *et al.* (2) recorded two hematological responses in four patients, but they also complained of the toxic manifestations of the treatments. Burchenal *et al.* (6) treated three patients with chronic lymphoid leukemia without any benefit and Meyer *et al.* (14) observed disappointing results in three patients following aminopterin therapy.

Hodgkin's Disease

Burchenal and associates published two reports in 1949 on the action of FAA on Hodgkin's disease: in one (7), they reported no useful results in seven patients and, in the other report (6), similar negative results in five patients; two years later (8), they recorded ten more failures. J. C. Wright *et al.* (32) described improvement in four of seven patients on FAA therapy, with one having a complete remission for seven months. Spigliati and Galardeschi (26) noted some hematological response in one of three patients on a combination of aminopterin and CF therapy. Sanchez Medal (21) treated three patients with amino-an-fol without any improvement, and Sullivan *et al.* (27) had no response in one patient on a combination of methotrexate and CF. Soto (24) had no response in a patient given FAA treatments, and Wilkinson (30) recorded the little value of aminopterin in the treatment of Hodgkin's disease. Schweisguth and Denoix (22) noted surprising long survivals in 34 children on a combination hormone-aminopterin routine.

Lymphosarcoma

In two publications in 1949, Burchenal and associates observed several brief responses in 10 patients with lymphosarcoma after treatment with 4-aminopteroyl glutamic acid (7) and, in a second report (6), they recorded no useful response to FAA in four other patients; in 1951 (8), these investigators classed three responses in seven children as good but, in 10 adults, there was no useful therapy. J. C. Wright (32) obtained a decrease in the size of lymph nodes in three of five patients on FAA therapy. Rosenberg *et al.* (18) noted that 41.7 percent of 24 children with lymphosarcoma had partial remissions with antimetabolites, chiefly FAA. Whiteside *et al.* (29) recorded good neurological response but no significant hematological change in five patients with leukemia or lymphosarcoma. Vignolo-Lutati (28)

induced a good remission lasting nine weeks in a patient treated with n-4(2-amino-4-hydroxypteridyl-6-methylamino)benzoylglutamic acid. Freireich *et al.* (10) described an objective response in one patient treated with 3′-5′-dichloramethopterin. Meyer and Newman (15) secured no clinical or significant hematological improvement in one patient on aminopterin, and Brown (5) noted a brief response in a patient with lymphosarcoma who received aminopterin and, later, cortisone.

Reticuloendothelosis

Burchenal and associates (8) described two good responses to FAA therapy in children with reticuloendothelosis, and Freireich *et al.* (10) reported two objective responses in two patients with reticulum cell sarcoma after 3′,5′-dichloramethopterin treatment. Sullivan *et al.* (27) induced some regression of lesions in a patient with reticulum cell sarcoma on a combination therapy of CF and methotrexate. Spigliati and Galaredeschi (26) found one patient with this neoplasm failed to benefit from the same therapy.

Multiple Myeloma, Mycosis Fungoides, and Polycythemia

J. C. Wright and associates (32) treated eight patients with multiple myeloma with FAA and recorded some slight benefit in four cases. In 1949, Burchenal *et al.* (6, 7) in two publications found these antimetabolites failed to benefit three patients with mycosis fungoides and one with multiple myeloma; in 1951, they (8) reported failure in another case of mycosis fungoides. Bell and Davis (1) noted a favorable response in one patient with polycythemia rubra vera treated with amino-an-fol.

Conclusion

It is concluded from published clinical reports that folic acid antagonists play a very minor role in the management of all malignant blood diseases except the acute leukemias.

Acknowledgments

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SELECTED ABSTRACTS

Transmission of Airborne Bacteria in Hospital Wards. Rubbo, S. D., Pressley, T. A., Stratford, B. C., and Dixson, S. *The Lancet* No. 7147:397 (1960). The problem of airborne microorganisms in hospital environs has spurred the investigation of the mechanisms by which these microorganisms may be transmitted. In general, hospital dust may be conveniently separated into two physical forms—large fiber particles that remain suspended in the air for only a short time after agitation and small fiber particles that remain airborne through the movement of air. Previous studies had shown—and it was verified in this study—that the airborne fibers were largely composed of cellulose. This would indicate that the source of these fibers was cotton sheeting, dressings, and personal clothing rather than the wool blankets, as had been supposed.

The authors found that the bacterial count obtained on settle-plates at 0, 3, 6, and 9 feet above the floor in three surgical wards of different construction was very nearly the same, particularly for bacteria of the staphylococcal type. Detectable fibers were found mostly at floor level although a few were found at the 9-foot level. Therefore, the authors postulated that large fibers seldom serve as vehicles for airborne organisms. Airborne transmission of bacteria largely takes place through the movement of free organisms or of organisms attached to microscopic fiber nuclei.

The Treatment of Edema With Spironolactone and Hydrochlorothiazide. Farrelly, R. O., Howie, R. N., and North, J. D. K. *Brit. Med. J.* No. 5195:339 (1960). It has been found that increasing aldosterone secretion plays a part in the development and maintenance of edema regardless of the disease. Spironolactone has been found to be an antagonist to aldosterone. The authors investigated the effect of spironolactone on patients in whom the aldosterone secretion would be expected to be greatly increased; namely, on those with active sodium retention but on a low-sodium diet with normal potassium intake. The diminishing response of patients to diuretics such as hydrochlorothiazide may be due to a competing effect of aldosterone and the diuretic until a steady state is reached in which sodium excre-

tion equals sodium intake. However, the patient may still be edematous.

In the study reported, after 4 days on hydrochlorothiazide, the patients were approaching a plateau of steady excretion of sodium and potassium. Upon the addition of spironolactone to the regimen, there was an increase in the sodium excretion and a fall in potassium excretion in six of seven patients.

The authors found that spironolactone is particularly effective in preventing potassium wastage during diuretic therapy, a known hazard of hydrochlorothiazide therapy. Spironolactone was not found to be particularly effective in removing edema fluid from the body but it did significantly increase the excretion of sodium.

The Control of Constipation in Submariners. Webrew, B. B., Elias, R. A., and Vogel, J. *U. S. A. F. Med. J. 11*:567 (1960). The control of constipation during prolonged submerged cruises is not a serious medical problem but it is important for the well-being of the crew. It had been noticed that there was a trend toward less frequent defecation as the submerged period progressed during two recent cruises of atomic powered submarines. Therefore, the authors undertook a study of the bowel habits and stool characteristics of a volunteer group of 59 men, for a period of 14 days during a snorkel cruise.

The group was divided so that 22 men received 100 mg. of dioctyl sodium sulfosuccinate daily in capsules, 22 men received a placebo capsule, and 15 men received no treatment and served as controls. Daily self-ratings were made regarding frequency of bowel movement, difficulty and pain associated with the passing of stools, relative firmness of stools, abdominal distress, amount of fluid and food intake, and frequency of urination.

The authors reported that the group treated with dioctyl sodium sulfosuccinate reported more frequent defecation, less firm stools, more abdominal discomfort, more pain associated with defecation, more fluid consumption, and more frequent urination. The placebo group also reported less firm stools. The 4 chronically constipated subjects showed no response to the dioctyl sodium sulfosuccinate.

The authors concluded that dioctyl sodium sulfosuccinate had some efficacy in the prevention of constipation but not in its treatment.

BOOK REVIEWS

Organic Reactions. Volume X, Roger Adams, Editor-in-Chief. vii + 563 pp. John Wiley and Sons, Inc., New York, N. Y., 1959. Price: $12.00.

The decennial volume of this well-established work is, again, a worthwhile addition to the reference literature of the organic chemist. Just three chapters are included: The Coupling of Diazonium Salts with Aliphatic Carbon Atoms, The Japp-Klingeman Reaction, and a rather extensive treatment (376 pages and over 1000 references) of the Michael Reaction.

It is rather unfortunate, whatever the reason may be, for the lapse of three or four years in literature coverage from preparation of the monographs to publication of the book. However, the usefulness of this volume is still exceptional as it, along with its predecessors, gives a complete, documented account of the reactions under consideration.

Volume X also includes an author and chapter index for all ten volumes and a subject index for Volume X.

A. R. GENNARO

Lipide Chemistry. Donald J. Hanahan. ix + 330 pp. John Wiley and Sons, Inc., New York, N. Y., 1960. Price: $10.00.

This text, by the major author with the contributions of Frank Gurd and Irving Zabin, represents the residue of the recent researches into the lipid field. The nine chapters deal with isolation and purification of lipids, phosphoglycerides, phosphoinositides, sphingolipids, phospholipids, assocation of lipids with proteins and naturally occurring lipoprotein systems.

Each chapter has an ample bibliography with references to the text. The literature is covered through 1958, with an occasional reference in 1959. It is unfortunate that the meager index (somewhat less than three pages) is not more extensive, especially if this book is intended for use as a text. The price may perhaps limit its use, but it should make a desirable text for a graduate course in lipid biochemistry.

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